REMARKS

Upon entry of the amendments, claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and new claims 60-62 are pending. Claims 1-14, 18-20, 23, 25-30, 32, 33, 36-41, 44, 46, 47, and 49-59 are canceled without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope in future continuation or divisional applications.

Independent claims 15, 21, 42, and 48 are amended, and new dependent claims 60-62 are added to further clarify the subject matter claimed. Support can be found in, for example, page 19, first full paragraph, in which the specification states that "ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included." The recited values 0.06, 0.09, 0.11, 0.16, and 0.21 are all explicitly disclosed in the above-referenced paragraph. Applicants submit that no new matter is introduced.

Applicants thank the Examiner for the withdrawal of all previous rejections of record. Applicants respectfully request the Examiner to consider and withdrawal the rejections in view of the arguments below.

Rejection Under 35 U.S.C. § 112, first paragraph - Written Description

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the Written Description requirement.

Specifically, while acknowledging that method claims directed to *treating arthritis or alleviating symptoms thereof*, comprising injecting a *fully human anti-TNFa antibody or antigen-binding fragment thereof*, in a dose of *0.1 mg/kg once per week*, the Examiner argues that similar methods reciting *any* dose within the 0.01 - 0.1 mg/kg range at *any* frequency not exceeding once per week allegedly fail to meet the Written Description requirement, because the specification allegedly fails to adequately describe the presently claimed invention. This is a new ground of rejection.

Solely to advance prosecution, Applicants have amended the pending independent claims and added new claims 60-62 to further clarify the subject matter claimed. In making these amendments, Applicants wish to state for the record that Applicants do not acquiesce to the reasoning of the rejection, and reserve the right to pursue claims identical or similar in scope to the claims prior to the above amendments, in this or a future continuation / divisional application.

Applicants submit that at least the currently recited ranges are adequately represented by the disclosed species, such as 0.1 mg/kg, especially in view of the data of 0.01 mg/kg and 0.5 mg/kg. See, for example, Figures 1, 4, and 5.

For instance, in Figure 5A, where inflammation data is presented for the tested agents (including D2E7) at various dose ranges, 0.1 mg/kg clearly gives rise to the same (if not better) efficacy than 0.5 mg/kg. The same result is obtained for "cartilage erosion" in Figure 5B (note that the 0.1 mg/kg and 0.5 mg/kg bars are both approaching zero). Further results were achieved in Figures 5C (vascularity) and 5D (bone erosion) when 0.1 mg/kg and 0.5 mg/kg are compared.

In view of these results, one of ordinary skill in the art would realize that efficacious results can be achieved for certain intermediate doses, such as 0.21, 0.16, or 0.11 mg/kg. On the other hand, given the relatively dramatic differences between 0.01 mg/kg and 0.1 mg/kg in Figures 5A-5D, one of ordinary skill in the art would further realize that efficacious results may also be attained at least for the 0.06 mg/kg intermediate dose, and almost certainly for the 0.09 mg/kg dose. Further, literal support for the claimed range of about 0.06-0.21 can be found in the specification at paragraph 83 of the published application.

Therefore, Applicants submit that at least the claims as amended satisfy the written description requirement. Reconsideration and withdrawn of the rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over ***Schattenkirchner*** (Presented at: The Annual Meeting of the European League Against Rheumatism (EULARO, Prague, Czech Republic, June 2001)), in view of ***den Broeder*** *et al.* (Rheumatology (Oxford) 41(6): 638-642, June, 2002, of record, or "den Broeder" hereinafter), ***Salfeld*** *et al.* (U.S. Pat. No. 6,258,562, of record, or "Salfeld" hereinafter), ***Kim*** *et al.* (Arthritis & Rheumatism 43(3): 473-484, March, 2000, or "Kim" hereinafter), and ***Stephens*** *et al.* (Antibody Therapeutics (1997), pp 317-340, eds. Harris *et al.*, CRC: Boca Raton, FL, or "Stephens" hereinafter). This is a new ground of rejection.

In making the obviousness rejection, the Examiner argues that Schattenkirchner teaches a method of treating arthritis using 0.5 mg/kg D2E7 on a weekly basis, but fails to teach weekly administration of 0.1 mg/kg of D2E7. However, the Examiner argues that den Broeder, Salfeld,

Kim, or Stephens provide motivation and reasonable expectation of success to lower the dosage level down by five folds to arrive at the presently claimed invention.

Applicants respectfully traverse the rejection to the extent it is maintained over the claims as amended.

In the sections below, Applicants will specifically address why none of the cited secondary reference can serve to make up the deficiency of Schattenkirchner.

The den Broeder Reference

The Examiner agrees with Applicants that the only certain conclusion that can be made from den Broeder is that, at least, the three treated patients were on the once per two weeks schedule, thus making the lowest average dose to be about 0.125 mg/kg per week (assuming the parameter "lowest average dose in mg/kg per week" has any scientific / clinical significance).

The Examiner also argues that den Broeder further provides motivation to lower the minimal dose for reasons such as minimizing cost and risks associated with TNFα suppression. The Examiner also points to the den Broeder statement that "one could speculate that even further reduction is possible for individual patients."

Applicants have argued previously that den Broeder does not teach or suggest how much lower the combined dosage and frequency can go without completely foregoing the benefit of the treatment.

In addition, Applicants submit an additional reason why one of skill in the art would not draw motivation from den Broeder to further lower the 0.5 mg/kg dose taught in Schattenkirchner, at least not by 2-5 more folds in accordance with the amended claims.

Applicants note that the patient population in the study described in den Broeder have been on D2E7 for at least two years and 6 weeks prior to the den Broeder study, with the last year on 3.0 mg/kg of D2E7. See page 639, towards the middle of the left column:

> Patients had originally been enrolled in a 6 week Phase I study. . . . Patients had subsequently been treated in an extension study for 2 yr with anti-TNF-α (adalimumab, D2E7 …) administered intravaneously. During the second year of this extension study, the patients had been treated with a fixed dose of 3.0 mg/kg…" (emphasis added).

Therefore, the den Broeder study is clearly designed to test the minimal maintenance dose after patients have already had their disease conditions under control through years of high

dose D2E7 treatment. Consistent with this view, the conclusion drew by den Broeder is "… clinical efficacy is maintained" (emphasis added). See last paragraph of den Broeder on p.641.

It follows that one of ordinary skill in the art, in view of the context of the den Broeder experiment, especially the patient population recruited for the study, would not have been motivated to use the lowest *maintenance dose* disclosed in den Broeder to modify the 0.5 mg/kg clinical dose used in Schattenkirchner, which applies to a more generalized patient population who had not undergone the years of treatment described in den Broeder.

Second, Applicants also note that the purpose of the den Broeder study was to titrate a minimal dose suitable for individual patients. Therefore, it explicitly *teaches away* from a "standard dosing schedule (used) in daily clinical practice" (page 639, top of left column), as is presently claimed.

den Broeder states, as the Examiner has also noticed, that "[t]here is marked variation in the individual dose of anti-TNF-α needed to maintain clinical efficacy" (page 641, last paragraph of the article). Because of this "marked variation," den Broeder criticizes that the "fixed doses" used in the "randomized controlled trials" lead to "standard dosing schedules in daily clinical practice" that will "result in gross under- and/or overtreatment" (paragraph bridging pages 638-639), and thus preaches "[t]ailoring treatment to the individual needs."

Therefore, reading den Broeder in its proper context, one of ordinary skill in the art would not extrapolate the results described specifically in den Broeder as appropriate for individual patients to the general patient population described in Schattenkirchner who are the subject of "standard dosing schedules in daily clinical practice," as this goes *against* the very teaching of den Broeder.

For substantially the same reason, one of ordinary skill in the art also would not have had a reasonable expectation of success in modifying the standard dosing schedule in Schattenkirchner to the "best-case-scenario" individual low dose in den Broeder calculated by the Examiner to arrive at the presently claimed invention. One of ordinary skill in the art would further have had no reasonable expectation of success in adapting a relatively low dose (that is still higher than the presently claimed dose) found to be effective in a few patients (as described in den Broeder) to a general patient population described in Schattenkirchner.

In summary, Applicants submit that den Broeder relates to maintenance dose in heavily treated patient population, and results from individual patients, and that den Broeder explicitly teaches away from the generalization of its disclosed low dose. Thus, den Broeder provides

neither motivation nor a reasonable expectation of success to further lower the dose disclosed in Schattenkirchner by 2- to 5-fold to arrive at the presently claimed invention.

The Salfeld Reference

Applicants' position is that **Salfeld fails to disclose "a low dose of 0.1 mg/kg at a frequency of once per week**." The Examiner has previously acknowledged (and still does not dispute) that "Salfeld recites … the range of 0.1-20 mg/kg, and that Salfeld recites this dosage range without concurrently reciting a frequency of administration."

Applicants also reiterate (which the Examiner does not dispute) that the only time an administration frequency is recited with a dose range in Salfeld is in Example 4, part D, section III (col. 43, lines 6-8), where a thrice a week frequency is used: "[e]ach group received three i.p. injections per week of the indicated treatments" (emphasis added). The minimal dose tested in this experiment is 1.5 mg/kg (col. 43, line 2).

Therefore, even assuming for the sake of argument that Salfeld indeed teaches that the dose range and administration frequency are results effective variables (a point with which Applicants disagree), the presently claimed combination of dose coupled with the administration frequency clearly falls outside of the range disclosed in Salfeld. As a result, optimizing the ranges in Salfeld would not lead one of ordinary skill in the art to arrive at the presently claimed invention.

The Schattenkirchner Reference (in view of Kim)

The Examiner argues that a further expectation of success comes from the Schattenkirchner reference itself, because the patients enrolled in that study "were not treatment naïve … and they had previously failed a mean of 3.5 DMARDs." Thus the Examiner argues that one of skill in the art "could reasonably expect to be able to titrate the dose of D2E7 for patients who are newly diagnosed and therefore have not already sustained irreversible joint damage (see Kim, page 473, Introduction)."

Applicants first note that, in order to make this argument stand, the Examiner must first import a "new patient" limitation into the pending claims. Applicants submit that the presently claimed invention is not limited to treating arthritis (or alleviate symptoms of arthritis) in newly

diagnosed patients. Rather, any individual in an arthritic patient population is the target for treatment and symptom relief.

Furthermore, even assuming for the sake of argument that the one of ordinary skill in the art would have been motivated (which Applicants do not concede) to further lower the Shattenkirchner dosage of 0.5 mg/kg for any patient, including a "new patient", one of ordinary skill in the art would have had no reasonable expectation as to how much lower an effective treatment dose can go. Would a further reduction of 20% considered unexpected? What results if it turns out to be a 1000-fold reduction? If the former is not, while the latter is, where is the boundary of this supposedly "routine titration / optimization"?

Therefore, Applicants submit that this argument of the Office Action is predicated on importing a limitation that is not in the claims, and the argument, *arguendo*, fails to show that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the presently claimed invention.

The Stephens Reference

In this new ground of rejection, the Examiner cites Stephens as a secondary reference as providing motivation and reasonable expectation of success for lowering the 0.5 mg/kg in Schattenkirchner to the presently claimed invention.

In the previous rejection, **the key point of contention was whether Stephens teaches the treatment of human RA with 0.1 mg/kg *humanized* anti-TNFα antibody CDP571**.

The Examiner asserted that it does, because of the following two quoted sentences on page 327, 4th paragraph of Stephens: "First infusion - *Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment with maximum patient response after 10 mg/kg . . . All patients who received CDP571 scored a reduction in pain scale by week 1*" (emphasis added).

Applicants argued that it does not, because there is no evidence of any symptom relief for the 0.1 mg/kg CDP571 treatment group described in Stephens that is commensurate with the required elements of the claims. Specifically, Applicants have argued, among other things, the following:

(1) Stephens does not show any results, let alone any alleviation of the symptoms recited in the claims, for the treatment group receiving 0.1 mg/kg CDP571 (see Tables 2 & 3 on

page 328 of Stephens). The whole section discussing the results after the **first infusion** never explicitly refers to any data in the 0.1 mg/kg group.

(2) The "dose-dependent effect" statement relied upon by the Examiner should be fairly read to refer only to the 1 mg/kg and 10 mg/kg groups, not the 0.1 mg/kg group.

(3) The 0.1 mg/kg treatment group was dropped all together in the second, third, and fourth injections.

(4) For the "all patients (pain scale reduction by week 1)" statement relied upon by the Examiner, even assuming, for the sake of argument, that it is not taken out of context, the significance of the observation is severely undermined by the fact that there is pain score reduction by week 1 in all groups, including the placebo group.

In the instant Office Action, the Examiner has deemed the above arguments non-persuasive for two reasons: (a) the above arguments do not comport with the literal teachings of Stephens; and (b) Applicants placed undue focus on results at 2, 4, and 8 weeks after a single injection of CDP571 at 1 or 10 mg/kg.

However, point (b) above does not appear to be related to the issue of whether Stephens teaches the treatment of human RA with 0.1 mg/kg of CDP571. Even assuming what the Examiner asserts regarding the 1 mg/kg group is all true, Applicants respectfully submit that the assertions have no bearing on the issue of treatment efficacy in the 0.1 mg/kg group. So does the Examiner's comments regarding the CRP data. Thus Applicants will only address point (a) below.

First, Applicants respectfully disagree with the Examiner's assertion on page 15 of the instant Office Action that "Stephens further teaches patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see page 327, 4th paragraph" (underline emphasis added).

The cited paragraph with the two most relevant sentences is quoted above. The term "dose-dependent effect" is only used in the first sentence, which sentence Applicants maintain refers to the 1 mg/kg and 10 mg/kg groups only, but not the 0.1 mg/kg group. The Examiner disagrees with this position, and questions why Stephens does not explicitly say the 0.1 mg/kg treatment group does not improve (as Stephens did for the placebo group).

Applicants respectfully submit that Stephens can properly make the "dose-dependent effect" statement, regardless of whether the 0.1 mg/kg group does or does not have a therapeutic

effect. For example, if the 0.1 mg/kg group does not have a conclusive effect, or simply has no effect at all, and Stephens knew it, Stephens could still properly make the conclusion, based on the 1 mg/kg and 10 mg/kg data, that there is "dose-dependent effect" of CDP571 treatment with maximum patient responses after 10 mg/kg. Therefore, contrary to the Examiner's assertion, Applicants' arguments concerning the "dose-dependent effect" statement do not contradicts the literal teachings of Stephens.

Applicants do not want to speculate as to exactly why Stephens does not provide an explicit statement (one way or the other) about the 0.1 mg/kg group data. However, Applicants note that Stephens did fail to mention that the placebo group also has a sizeable pain score reduction after week 1 (which is apparent from the data in Table 2) when Stephens stated that "[*a*]*ll patients who received CDP571 scored a reduction in pain scale by week 1.*"

In fact, even assuming for the sake of argument that this "all patients" sentence above does pertain to the 0.1 mg/kg treatment group (which Applicants do dispute, see argument in the previous response), this is the only literal teaching in Stephens that explicitly pertains to the efficacy of the 0.1 mg/kg treatment group. Aside from having shown no actual data for the extent of the reduction, any alleged efficacy of the 0.1 mg/kg treatment group is severely undermined by the data in Table 2 showing that the placebo group also had a sizeable pain score reduction after week 1. Applicants note that the Examiner does not disagree with this argument.

Applicants submit that this argument also does not contradicts the literal teachings of Stephens, contrary to the Examiner's assertion. Applicants did not argue that the Stephens "all patient" statement quoted by the Examiner is incorrect. Instead, Applicants merely brought this statement within its proper context - in view of the control / placebo - as is required to correctly interpret a scientific result.

In summary, the Examiner deemed Applicants' arguments regarding Stephens non-persuasive on two specific grounds, one of which appears to be unrelated to the issue of contention, while the other appears to be without factual basis, because Applicants' arguments did not contradict either of the two quoted "literal teachings of Stephens." Therefore, Applicants respectfully request the Examiner to reconsider the disclosure of Stephens in view of the arguments herein and those presented in the previous response.

Relating to this, Applicants note that the Examiner's current position appears to be that Stephens "would undoubtedly be recognized by one of ordinary skill in the art to represent at least one published attempt at using a dose of 0.1 mg/kg anti-TNFα antibody…" Applicants do

not disagree with this position. However, an "attempt" is, in the absence of any proven efficacy, nothing more than an attempt. It does not offer one of skill in the art motivation or reasonable expectation of success anything more than the placebo does. In fact, Applicants respectfully submit that the lack of any conclusive data for the 0.1 mg/kg data, in combination with the marginally effective effect from the 1 mg/kg treatment group, would likely discourage one of skill in the art not to lower the 0.5 mg/kg Schattenkirchner dose any further, let alone 2- to 5-fold further.

Based on the *Graham* factual findings above, Applicants submit that **den Broeder** relates to maintenance dose in highly treated individual patients, and teaches away from the generalization of its disclosed low dose; **Salfeld** suggests a wide dosage range of between 0.1-20 mg/kg, with the only relevant disclosure about frequency being three times a week, and each time at doses at least about 8-300 fold higher than the claimed range; **Stephens** provides no evidence that the *tested* 0.1 mg/kg dose is actually *effective* compared to placebo at alleviating any of the symptoms required by the claims; and **Schattenkirchner and Kim** are not relevant since the claims are not limited to newly diagnosed patients and there is no teaching or suggestion in either reference regarding whether to lower a dose and, if so, to what extent. Therefore, none of the cited art provides motivation or reasonable expectation of success to modify the primary reference and arrive at the claimed invention. A *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over **den Broeder** in view of **Salfeld**. This is a new ground of rejection. The Examiner argues that it would have been obvious to further lower the dose (0.25 mg/kg per 2 weeks) in den Broeder so as to minimize cost and the risk of infection resulting from TNFα suppression, in view of the Salfeld teaching to adjust the dose and frequency as a result effective variable. Applicants respectfully disagree.

Both references are discussed in detail above.

Since den Broeder relates to maintenance dose in highly treated individual patients, and teaches away from the generalization of its disclosed low dose (see above), Applicants submit that one of ordinary skill in the art would neither be motivated nor have a reasonable expectation of success to further lower the "best-case-scenario" individual patient result and generalize the

dose to the "standard dosing schedules in daily clinical practice," against the very teachings of den Broeder itself. Therefore, a *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

Claims 15-17, 21, 22, 24, 31, 42, 43, 48, and 57-59 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Le *et al.* (U.S. Pat. No. 7,166,284, or "Le #1" hereinafter) or Le *et al.* (U.S. Pat. No. 7,138,118, or "Le #2" hereinafter), as evidenced by Kaymakcalan *et al.* (Clinical Immunology 131: 308-316, 2009) and Shealy *et al.* (mAbs 2:4, 1-12, July / August 2010, or "Shealy" hereinafter).

Alternatively, the same claims, in addition to claims 34, 35, and 45, are allegedly unpatentable under 35 U.S.C. § 103(a) as obvious over Le #1 or Le #2 either in view of den Broeder, Salfeld, as evidenced by Kaymakcalan and Shealy.

Since claims 58 and 59 have been canceled, their rejections are rendered moot.

For the remaining claims, the Examiner evoked the Doctrine of Claim Differentiation concerning claims 1 and 11 of Le #2, and argues that Le #2 encompasses a subgenus of methods of treatment using 0.1-0.5 mg/kg human anti-TNFα antibody. The Examiner went on to argue that K_d and IC_{50} are also taught in Le #2. Although the Examiner agrees that Le #2 does not explicitly teach the recited k_{off} rate constant for its human antibody, the Examiner argues that one antibody within the scope - the chimeric monoclonal antibody infliximab - has remarkably similar k_{off} rate constant compared to adalimumab and golimumab.

Thus, the Examiner concludes that, in making the human anti-TNFα antibody within the scope of Le #2 claims, one of skill in the art "would necessarily be making an antibody having the biophysical characteristics recited in the instant claims."

Applicants respectfully traverse this rejection on two separate grounds.

First, Applicants submit that the disclosed genus in Le #2 cannot anticipate the claimed species, because one of skill in the art cannot "at once envisage" the claimed species based on the broad genus disclosure.

Specifically, Applicants note that claim 1 of Le #2 does not have a dosage frequency limitation. Applicants further note that claim 12, which appears to be related to frequency, has

numerous combinations of dose and frequency. Thus Le #2 appears to disclose a genus that could, at best, potentially encompass the specific species of the claimed dose-frequency combination.

Applicants have argued in the last response that, when discussing Genus-Species anticipation situations, MPEP 2131.02 states that: "[w]hen the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990)." Applicants submit that *Ex parte A* applies here, and that Le cannot anticipate the pending claims because one of ordinary skill in the art cannot "at once envisage" the presently claimed invention in view of the disclosure of Le.

Specifically, Le purportedly disclose multiple dosage levels (with a broad range of 0.01 to 50 mg/kg (claim 11), plus **19 specific possibilities** within the range: 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 mg/kg) and multiple administration intervals (including at least **50 specific possibilities**: on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20). Applicants note that the disclosed range contains an infinite number of possibilities, especially within the alleged range of 0.1-0.5 mg/kg purportedly disclosed under the Doctrine of Claim Differentiation. The allegedly anticipated combination - 0.1 mg/kg at once per week - is merely one out of about 1000 (if not an infinite number) of possible combinations. Therefore, Applicants submit that the presently claimed invention cannot be "at once envisaged" by the broad disclosure of Le. Thus, Le cannot anticipate the presently claimed invention.

Applicants note that the Examiner's argument in the instant Office Action concerning anticipation with "sufficient specificity" (MPEP 2131.03) only applies when prior art teaches a range that overlaps or touches a claimed range.

Second, regarding the k_{off} rate constant and the recited symptom relief requirements, the Examiner appears to be making an inherency rejection by using the term "necessarily."

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, it must be clear on the record that the missing descriptive matter is necessarily present in the description in the reference, and that it would be so recognized by persons of

ordinary skill. *Continental Can Co. USA, Inc. v. Monsanto Co.,* 948 F. 2d 1264, 1268-69 (Fed. Cir. 1991).

As stated in *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (CCPA 1981):

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. [Citations omitted.]

This standard is clearly ***not*** met here. Take the k_{off} rate constant for example, the parameter $K_d = k_{off} / k_{on}$. Thus mathematically, the same K_d can be achieved through infinite combinations of k_{off} and k_{on} values, each can be large or small, so long as their *ratio* remains the same. It cannot be said that the k_{off} value is necessarily 1×10^{-3} s^{-1} or less, as recited in the claims, simply because the K_d value may be the same. This conclusion does not change (for the human antibody allegedly within the scope of Le #2 claim 1), simply because one specific chimeric antibody within the same broad claim scope - infliximab - has similar k_{off} rate constant as the claimed human antibody. This constitute a separate and independent ground that the anticipatory rejection cannot stand.

Applicants submit that the anticipatory rejection based on Le #1 is substantially the same, and the same arguments above applies with equal force.

Reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 102 are respectfully requested.

In the alternative, the Examiner argues that the claims would have been obvious since one of skill in the art would have been motivated to modify the teachings of either Le #1 or Le #2 (*i.e.*, the alleged "moderate success by administration of a single dose of 1 mg/kg infliximab in Example XX") to arrive at the claimed invention. In making this rejection, the Examiner again relied on den Broeder to provide motivation and reasonable expectation of success.

Applicants, however, cannot find where in Example XX of either Le #1 or Le #2 is the teachings about using 1 mg/kg infliximab. For example, in Le #1, col. 60, lines 9-12 clearly indicate that, among the 9 patients treated in the open-label (*i.e.*, no control / placebo group) non-blinded study, 5 received two injections on day 1 and day 15, at a dose of 10 mg/kg each time, while 4 received four injections on days 1, 5, 9, and 13, at a dose of 5 mg/kg each time.

Thus, regardless of whether the result is "modest," the dosage used is 50-100 times higher than the presently claimed invention. Applicants respectfully submit that there is no

motivation or reasonable expectation of success to lower even the 5 mg/kg dose by 50-fold in order to reach the claimed invention, especially in view of the deficiency of den Broeder discussed above.

Therefore, Applicants submit that a *prima facie* case of obviousness has not been established. Reconsideration and withdrawal of the obviousness rejections are respectfully requested.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 449-6500.

The Commissioner is hereby authorized to charge any fees associated with the filing of this communication to our Deposit Account No. **50-4876**, from which the undersigned is authorized to draw under Order No. **117813-99302**.

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Respectfully submitted,

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